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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/749,118 | 12/30/2003 | Richard L. Boyd | 286336.151US1/NOR-012CP2 | 3277 |

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| EXAMINER | |
|---|---|
| LI, QIAN JANICE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 04/15/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/749,118 | BOYD, RICHARD L. | |
| | Examiner | Art Unit | |
| | Q. JANICE LI | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *34,46,51,53-59,61-78,84-86,91 and 101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,32,33,36-40,47-50,80-82,92-98 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 29,30,32-34,36-40,46-51,53-59,61-78,80-82, 84-86,91-98,101,103.

**DETAILED ACTION**

The examiner assigned to review your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1633.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/10/09 has been entered.

Claims 1-28, 31, 35, 41-45, 52, 60, 79, 83, 87-90, 99, 100, 102 have been canceled. Claims 29, 30, 32-34, 36-40, 46-51, 53-59, 61-78, 80-82, 84-86, 91-98, 101, 103 are pending in the application. Claims 34, 46, 51, 53-59, 61-78, 84-86, 91, 101 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 29, 30, 32, 33, 36-40, 47-50, 80-82, 92-98, 103 are under current examination.

Upon search and consideration, previous rejections are withdrawn, and new grounds of rejection are necessitated and appeared below.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 32, 33, 36-40, 47-50, 80-82, 92-98, 103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to a method of treating an autoimmune disease in a patient including humans. The method comprises depleting T cells in the patient,

reactivating the thymus of the patient, and optionally further transplanting stem cells, dendritic cells, or combination thereof into the patient.

In view of the disclosure, the specification surveys changes in thymus, spleen and lymph nodes after cyclophosphamide-mediated T cell depletion and castration (e.g. figures 7-12), in examples 6-12, the specification uses approaches such as T cell depletion, sex steroid ablation, stem cell transplantation and observes impact on thymus and lymphocytes. However, these are not autoimmune disease models, and there is no clear evidence of effectively treating any autoimmune disease using the aforementioned means. Example 16 is entitled "Effects of castration on NOD and NZB mice", wherein the applicant reported surgically ovarectimising female NOD mice, which lead to a reduced rate of onset of diabetes. Here, only castration was performed on female NOD mice, T cell depletion and stem cell transplantation were not involved. As to NZB mice, the specification reports a marked increase in total thymocytes and spleen cells 4 weeks after castration. However, the specification fails to mention the effect on the autoimmune disease associated with the NZB mice. No T cell depletion or stem cell transplant is reported in this instance. As such, the disclosure of the specification fails to provide an enabling disclosure to support the full scope of the claimed invention.

Turning to the state of the art pertaining to treating autoimmune diseases through T cell modulation, it was still under development and highly unpredictable at the time of instant priority date. The claims broadly embrace any autoimmune disease, however, not every autoimmune disease is T cell-mediated, and more often than not, each involves different mechanisms. The specification fails to provide an enabling disclosure

for the broadly claimed subject matter from the sole working example 16. Although it was known in the art that insulin-dependent diabetes mellitus (IDDM) is a T cell-mediated disease, the exact mechanism and how to manipulate the immune system so as to control the autoimmune disease state were still unclear, and art were replete with contradictory findings. For example, *Anderson* (Autoimmunity 1993;15:113-22) teaches insulin-dependent diabetes in NOD mice is a Th2 cell-mediated event, not a Th1 cell-mediated event (see e.g. the abstract), hence, generally deleting all T cells as instantly claimed may not be beneficial for treating diabetes. *Anderson* also reports that IL-7 was expressed in the islet at very high levels in IDDM mice, hence further supplementing IL-7 as now claimed for treating diabetes is unlikely to be beneficial. On the other hand, *Gombert* (C.R. Acad Sci. Paris 1996;319:125-9) reports NOD mice were found to have a marked deficit in the number and functional capacity of a subset of thymocytes, which leads to deficiency in IL-4 production, while supplying IL-7 completely corrected the deficiency (see the abstract). *Sai* (Clin Exp Immunol 1994;97:138-45) reasoned since the IDDM is a T cell mediated disease, T cell depletion may influence the course of IDDM. *Sai* injected cyclosporine (depleting T cell) at birth and found in cyclosporine treated female NOD mice, the onset of diabetes was earlier and cumulative incidence was higher in female NOD mice, and while T-cell depletion has dramatically enhanced incidence of diabetes in male NOD mice (see e.g. tables and figures). Apparently, according to *Sai*, depleting T cell alone has promoted rather than reduced the incidence of diabetes in NOD mice. Consistent with this finding, *Akhtar et al.* (J Exp Med 1995;182:87-97) reported that several *autoreactive* CD4+ T cell clones reactive to auto-

antigens, can also suppress adoptive transfer of the IDDM, and hence *suppress* the development of autoimmune diabetes in NOD mice (e.g. figures 4, 6, and table 3). *Cameron et al.* (Diabetes Metab Rev 1998;14:177-85) concludes the NOD mouse model of IDDM has suggested an important mechanism, i.e. the autoimmune diabetes is a failure in immune regulation. Many immunological mechanisms such as T-cell anergy and deficiency in T-cell mediated suppression contribute to the induction of diabetes. Given such complicated role of T cells in the development and continuance of the autoimmune diabetes, the disclosure of the specification is insufficient to provide an enabling disclosure for what is now claimed.

Turning to the state of the art pertaining to treating autoimmune diseases through castration and thymus manipulation, it was still under development and the record was replete with contradictory findings at the time of instant priority date. The only common consent is that castration has certain influence on the development of autoimmune diabetes, and female NOD mice develop the disease more frequently than male NOD mice. For example, *Fitzpatrick et al.* (Endocrinol 1991;129:1382-90) reports castration at weaning led to a significant increase in the prevalence of diabetes in NOD males, but a tendency to a decreased prevalence was observed in NOD females, while *Verheul et al.* (Clin exp Immunol 1986;63:656-62) reports sex, gonadectomy (castration in male mice) does not influence the development of IDDM in BB rat, an adequate model for human IDDM. *Roubinian et al.* (J Exp Med 1978;147:1568-83) reports prepubertal castration of male B/W mice caused an essentially female pattern of disease with 100% mortality at 11 month, whereas prepubertal castration of female B/W mice markedly reduced the

development of IgG antibodies to PolyA. Apparently, accordingly to the cited art of record, castration only asserts protective effect on the development of autoimmune disease in female, if any.

Instant claims assert treating an autoimmune disease with any kind of stem and progenitor cells such as epithelial stem cells, and dendritic cells. Although it was known in the art that autoimmune diseases may be associated with stem cell deficiency (*Marmont*, Haematol 1998;83:733-43), neither the art nor the specification teaches that dendritic cells, or epithelial stem cells are capable of treating autoimmune diseases. In fact, *Rosmalen* reports (Lab Invest 2001;81:231-9) castration by orchidectomy led to increased mega-islet formation and *dendritic cell infiltration* (e.g. figures 4 & 5). Apparently dendritic cells contribute to the pathology of autoimmune diabetes. It was not known and the specification fails to teach that administration of dendritic cells could ameliorate the autoimmune diabetes. In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references, and it would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Claims 38 and 93 are directed to transplanting autologous stem cells for treating diabetes, however, *Ikehara* (Intl J Mole Med 1998;1:5-16) teaches normal but not autologous diabetic hematopoietic stem cells alleviate IDDM.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30, 32, 33, 36, 37, 39, 40, 92, 94-98, 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick et al.* (Endocrinol 1991;129:1382-90).

*Ikehara* teaches a method of treating an autoimmune disease such as the non-insulin-dependent diabetes mellitus (NIDDM, § 13), the method comprises lethally irradiate obese insulin-resistant KKAy mice known to resemble obesity-linked type 2 diabetes in humans (=depleting T cells in the patient), and reconstituted mice bone marrow with T-cell depleted bone marrow mononuclear cells comprising CD34+ hematopoietic stem cells (=administering stem cells to the patient). *Ikehara* acknowledges it was known in the art that the thymus plays a crucial role in the mechanism of autoimmune diseases, but did not study the association between thymus and the NIDDM.

*Fitzpatrick* supplemented the deficiency by establishing it was known in the art castration at weaning lead to a decreased prevalence to diabetes in female NOD mice (see abstract and figures).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Ikehara* and *Fitzpatrick* for preventing or treating diabetes with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the combined approach may prove to better control the diabetes. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick et al.* (Endocrinol 1991;129:1382-90) as applied to claims 29, 30, 32, 33, 36, 37, 39, 40, 92, 94-98, 103 above, further in view of *Jett et al.* (Breast Cancer Res Treat 1999;58:131-6).

The combined teachings of *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick* does not use a chemical such as leuprolide for castration.

*Jett* supplemented the deficiency by establish it was well known in the art that leuprolide is as effective as surgical castration (e.g. the abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Ikehara* in view of *Fitzpatrick* using chemical castration as taught by *Jett* with a reasonable expectation of success. Given several means known in the art for therapeutic castration, the limitation falls within bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 80, 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick et al.* (Endocrinol 1991;129:1382-90) as applied to claims 29, 30, 32, 33, 36, 37, 39, 40, 92, 94-98, 103 above, further in view of *Cava et al.* (Curr Dir Autoimmune 1999;1:56-71).

The combined teachings of *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick* does not teach to include cytokines in the therapy.

*Cava* supplemented the deficiency by establish it was well known in the art that cytokines play a role in regulating autoimmune disease such as IDDM (e.g. page 65).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Ikehara* in view of *Fitzpatrick* to include appropriate cytokines supplementing stem cell transplantation and castration as taught by *Cava* with a reasonable expectation of success. Given the knowledge in the art as taught by *Cava*, it was within the levels of the skilled to determine which cytokine to use. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 80, 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick et al.* (Endocrinol 1991;129:1382-90) as applied to claims 29, 30, 32, 33, 36, 37, 39, 40, 92, 94-98, 103 above, further in view of *Simpson et al.* (Growth Hormone IGF Res 1998;8:83-95).

The combined teachings of *Ikehara* (Intl J Mole Med 1998;1:5-16) in view of *Fitzpatrick* does not teach to include growth factors in the therapy.

*Simpson* supplemented the deficiency by establish it was well known in the art that growth factors such as IGF-I play a role in regulating IDDM (e.g. page 65).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Ikehara* in view of *Fitzpatrick* to include appropriate growth factor(s) supplementing stem cell transplantation and castration as taught by *Simpson* with a reasonable expectation of success. Given the knowledge in the art as taught by *Simpson*, it was within the levels of the skilled to determine which growth factor to use. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

*/Q. JANICE LI/*
*Primary Examiner, Art Unit 1633*

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
April 13, 2009